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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/623,930	07/21/2003	Vicki Bowman Vance	9536-3	6465

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EXAMINER	
KUMAR, VINOD	
ART UNIT	PAPER NUMBER
1638	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/623,930	VANCE ET AL.	
	Examiner	Art Unit	
	Vinod Kumar	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1-19,21,22,24 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,23 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/03/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of objections and rejections

1. Office acknowledges the receipt of Applicant's request for continued examination (RCE) filed on January 3, 2007. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1-26 are pending. Claims 20, 23 and 26 are being examined in this Office action.

2. The rejection of claims 20, 23 and 26 under 35 U.S.C. 103(a) is withdrawn in view of claim amendment.

Claim Objections

3. Claims 20 and 23 are objected to because of the following informalities:

In claim 20, lines 5-6, insert --sequence-- after "miRNA" and before "endogenous".

In claim 23, line 6, insert --sequence-- after "miRNA" and before "endogenous".

Appropriate action/correction is required.

Claim Rejections - 35 USC § 112

4. Claims 20, 23 and 26 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a plant cell or plant transformed with an miRNA precursor construct comprising a promoter operably linked with a nucleotide sequence encoding a plant miRNA 167 or miRNA 171 precursor sequence which is

modified to contain a non-native miRNA sequence replacing the native or endogenous miRNA sequence in said miRNA precursor sequence, and wherein said non-native miRNA sequence is complementary to a portion of a target sequence of interest expressed from the plant genome, does not reasonably provide enablement for a plant cell or plant transformed with an miRNA precursor construct comprising any plant miRNA precursor sequence which is modified to contain an non-native (exogenous and heterologous) sequence replacing the native miRNA sequence in said plant miRNA precursor sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reasons of record stated in Office actions mailed on May 16, 2006 and October 31, 2006. Applicants traverse the rejection in the paper filed January 3, 2007.

Applicants argue that amended claims 20, 23 and 26 recite plant miRNA precursors, and plant miRNA precursors occur naturally in plants and can be isolated using techniques well known at the time of filing. Applicants further argue that modified plant miRNA precursors have been shown repeatedly to work in post filing publications, as described in specification and further described in Applicant's declaration filed in the paper of January 3, 2007. Applicants further argue that routinely used assays can be carried out to screen for operable miRNA precursor constructs (response, last paragraph bridging the pages 7 and 8).

Applicant's arguments were fully considered but were not found to be persuasive.

It is noted that claims 20 and 23 are directed to any plant miRNA precursor, comprising a non-native (heterologous) miRNA sequence which replaces the native (endogenous) miRNA sequence within said miRNA precursor sequence, and wherein said non-native miRNA sequence is complementary to a portion of a target sequence. Furthermore, it is also noted that, claims 20 and 23 also encompass plant miRNA precursors modified to comprise more than one non-native miRNA sequences which replace the native miRNA sequence in said plant miRNA precursor.

The instantly claimed invention requires designing a non-natural miRNA precursor by modifying any naturally occurring plant miRNA precursor. Neither the related art at the time claimed invention was made nor the specification provides guidance on designing an artificial or non-natural miRNA precursor comprising a non-native nucleotide sequence which replaces the native miRNA sequence in said precursor, and wherein said non-native nucleotide sequence is complementary to a target sequence of interest. Furthermore the specification does not provide guidance on whether said artificial or non-natural precursor would under go normal biogenesis to produce a miRNA upon its expression in a transformed plant.

In response to Applicant's 1.132 declaration filed in the paper of January 3, 2007, wherein Applicant asserts that the specification describes a general strategy to make "designer miRNAs" (1.132 declaration, page 3, lines 24-31), it is emphasized that designing an artificial or non-natural miRNA precursor requires use of computational rules, such as thermodynamic structure profiling to predict an miRNA precursor molecule with most favorable structure in solution. See for example, Krol et al. (JBC,

279:42230-42239, 2004), who clearly teach relevance of free energy rules in designing an artificial miRNA precursor molecule. See in particular, abstract; Figures 1-3, 6. Furthermore, Krol et al. teachings also imply that random sequence mismatches within the miRNA sequence of an artificial miRNA precursor design would influence the free energy of the precursor molecule, and which may negatively impact biogenesis of said precursor when expressed in a cell (page 42238, 2nd column). Neither the related art at the time of filing nor the specification provide guidance on how a non-native miRNA sequence within an artificial miRNA precursor design would have to be modified by introducing mismatches to predict a most favorable structure with lowest free energy when expressed in a plant cell. In the absence of such guidance, undue experimentation would have been required at the time claimed invention was made to determine how to modify any naturally occurring plant miRNA precursor so that modified miRNA precursor forms a stable structure and is capable of under going normal biogenesis to produce desired gene silencing effect when expressed in a plant cell or plant.

Furthermore, it is important to note that bulge(s) of a miRNA precursor play an important role in the overall recognition and processing of miRNA precursors. For example, see Alvarez et al. (The Plant Cell, 18: 1134-1151, 2006) who teach that designing an artificial or synthetic miRNA 164b precursor molecule would require introducing mismatch into the miRNA complementary sequence at specific site to mimic the predicted stem of miRNA precursor, assuming the bulges in the miRNA 164b backbone contain essential recognition and processing information (see, in particular

Figures 2 and 3). The specification and Applicant's 1.132 declaration of January 3, 2007, provide guidance on introducing mismatches in the non-native miRNA at the same sites as the native miRNA so that newly designed miRNA precursor mimics the secondary structure of the naturally occurring miRNA precursor. However, it must be emphasized that instant claims encompass replacing a native miRNA sequence in a naturally occurring plant miRNA precursor with any non-native nucleotide sequence of which is complementary to a target sequence of interest. The instant claims encompass introducing non-native sequences that could be of any length and base composition. The specification does not provide guidance on designing an artificial miRNA precursor of any length and of any base composition. In view of claim breadth, one skilled in the art would not know where else mismatches can be tolerated within the non-native miRNA design without undue experimentation. In the absence of guidance, undue experimentation would have been required at the time claimed invention was made to determine where to introduce such mismatches in the miRNA sequences of different miRNA precursor designs, so that the artificial miRNA precursor molecule is capable of undergoing normal biogenesis upon its expression in a plant.

Furthermore, it is noted that plant miRNA genes also exist in clusters. See for example, Mica et al. (Journal of Experimental Biology, 57:2601-2612, 2006) who teach existence of miRNA gene clusters in rice, maize etc. Furthermore, Lee et al. (The EMBO Journal, 21:4663-4670, 2002) teach that a single promoter may drive transcription of the clustered miRNA genes to produce nascent polycistronic transcripts, which would require additional unknown processing steps to produce pre-miRNAs. The

specification does not provide guidance on polycistronic miRNA precursors (expressed from clustered miRNA genes) which would be modified to contain at least one non-native miRNA sequence by replacing the native (endogenous) miRNA sequence in said polycistronic miRNA precursor. In the absence of such guidance, undue experimentation would have been required at the time claimed invention was made to determine how to design a plant miRNA precursor derived from clustered miRNA genes, and comprising replacing a miRNA sequence endogenous to said plant miRNA precursor with a non-native miRNA sequence, so that the artificial miRNA precursor molecule is capable of undergoing normal biogenesis upon its expression in a plant.

Furthermore, Applicant's attention is drawn to Example 4 of specification (pages 33-34), wherein prophetic direction is provided for the following: a) a GUS miRNA precursor designed by replacing miRNA 167 with a sequence (SEQ ID NO: 1) which is fully complementary to bases 9978-1000 of the GUS coding region, and which results in decreased GUS expression when expressed in a transgenic plant carrying GUS transgene, b) a GUS miRNA precursor wherein the GUS sequence chosen for the miRNA is complementary to a different region of the GUS mRNA coding region, and wherein increased GUS expression results in plants comprising the GUS transgene and miRNA precursor. The specification does not teach the differences between these two miRNAs, both of which are complementary to the GUS coding region, but which result in opposite effects on GUS expression. Example 4 also prophetically discusses a GUS miRNA precursor that is designed by replacing miRNA 167 with a sequence which is not completely complementary to a GUS coding region, and which is supposed to result

in decreased GUS expression when expressed in a transgenic plant carrying GUS transgene. However, the declaration filed January 3, 2007 indicates that sequences opposite the artificial miRNA are to be modified to maintain secondary structure in the stem, to stay within the context of the natural miRNA (item 5). The specification appears, then, to be teaching a designer miRNA precursor that will not be properly processed. It is also noted that the declaration is inconsistent with the prophetic guidance in the specification. The specification does not provide guidance on how to determine whether a plant miRNA precursor design would require replacing the native miRNA with a sequence which is either fully or partially complementary to a portion of the target sequence of interest, so that said precursor undergoes normal biogenesis to produce desired gene silencing effect when expressed in a plant. In the absence of adequate guidance, undue experimentation would have been required by a skilled artisan to determine how to design any non-natural plant miRNA precursor comprising replacing its native miRNA with a non-native sequence which is complementary to a target sequence of interest, so that said precursor undergoes normal biogenesis to produce desired gene silencing effect upon its expression in a plant.

Furthermore, it is noted that claims 20 and 23 encompass replacing endogenous miRNA sequence in a plant miRNA precursor with more than one non-native miRNA sequences. Neither the state of art at the time claimed invention was made nor the specification provides guidance on designing artificial miRNA precursor comprising replacing native miRNA sequence with more than one non-native miRNA sequences as encompassed by claims. This is especially important, as Applicants have argued that

secondary structure needs to be preserved. In the absence of any guidance, undue experimentation would have been required by a skilled artisan to determine how to modify a plant miRNA precursor by replacing the miRNA sequence native to said precursor with more than one non-native miRNA sequence(s) and which are complementary to a target sequence of interest, so that the artificial miRNA precursor molecule comprising more than one non-native miRNA sequences is capable of undergoing normal biogenesis upon its expression in a plant.

It is important to note that the issue is *not* whether experimentation was required at the time claimed invention was made to determine how to isolate plant miRNA precursor sequences. The issue is how to predict a stable non-natural miRNA precursor design so that said non-natural miRNA precursor undergoes normal biogenesis upon expression in a plant, and whether the experimentation required was undue at the time claimed invention was made, based upon the various factors previously discussed and further outlined as above.

In the absence of adequate guidance at the time of filing, it is maintained that undue experimentation would have been required by a skilled artisan to determine how to design (make) any plant miRNA precursor comprising at least one miRNA sequence which is non-native to said precursor, and complementary to a target sequence of interest, so that when expressed in a transgenic plant said modified plant miRNA precursor undergoes normal biogenesis to produce desired gene silencing effect in said transgenic plant. See Genentech, Inc. v. Novo Nordisk, A/S, USPQ2d 1001, 1005 (Fed.

Cir. 1997), which teaches that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention.

5. Claims 20, 23 and 26 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention at the time of filing for the reasons of record stated in Office actions mailed on May 16, 2006 and October 31, 2006. Applicants traverse the rejection in the paper filed January 3, 2007.

Applicants argue that claims 20 and 23 are amended to recite plant miRNA precursors and thus meet written description requirements. Applicants cite declaration filed in the paper of January 3, 2007 to support their argument (response, page 8, lines 19-24).

Applicant's arguments were fully considered but were not found to be persuasive. It is noted that claims 20 and 23 are directed to any miRNA precursor derived from any plant species, comprising a non-native miRNA sequence replacing the native (endogenous) miRNA sequence, wherein said non-native (exogenous, heterologous) miRNA sequence is complementary to a portion of a target sequence. The specification does not have adequate written description for the genus of plant miRNA precursor sequences comprising at least one non-native miRNA sequence which replaces native miRNA sequence of said precursor, and is complementary to a target sequence of interest under current written description guidelines. Applicants have failed to describe

undisclosed structures of their broadly claimed genus, and one skilled in the art cannot reliably predict these structures based on the disclosure of miRNA 167 and miRNA 171 precursor. The claims encompass structures of a broadly claimed genus whose function has not been correlated with regulating the expression of a target sequence of interest when expressed in a plant cell or plant. Applicants have failed to describe common functional domains or elements shared by the undisclosed structures of their broadly claimed genus. Thus, it is evident that Applicant's broadly claimed genus was not reduced to practice. Accordingly, there is lack of adequate description to inform a skilled artisan that applicant was in possession of the claimed invention at the time of filing.

The Federal Circuit has recently clarified the application of the written description requirement. The court stated that a written description of an invention "requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The court also concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of; is not a description of that material." Id. Further, the court held that to adequately describe a claimed genus, Patent Owner must describe a representative number of the species of the claimed genus, and that one of skill in the art should be able to "visualize or recognize the identity of the members of the genus." Id.

Finally, the court held:

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. Id.

See also MPEP Section 2163, page 174 of Chapter 2100 of the August 2005 version, column 1, bottom paragraph, where it is taught that

[T]he claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

See also Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ 2d 1016 at 1021, (Fed. Cir. 1991) where it is taught that a gene is not reduced to practice until the inventor can define it by "its physical or chemical properties" (e.g. a DNA sequence).

Also see in re Curtis (69 USPQ2d 1274 (Fed. Cir.2004), where the court held that there was sufficient evidence to indicate that one of ordinary skill in the art could not predict the operability of other species other that the single one disclosed in the specification. The court held that a disclosure naming a single species can support a claim to a genus that includes that species if a person of ordinary skill in the art, reading the initial disclosure, would "instantly recall" additional species of the genus already "stored" in the minds, but if other members of the genus would not "naturally occur" to a

person of ordinary skill upon reading the disclosure, then unpredictability in performance of species other than specifically enumerated defeats claims to the genus.

For at least these reasons and the reasons of record stated in the previous Office Action, the requirement for written description has not been met.

Summary

6. Claims 20, 23 and 26 are rejected.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vinod Kumar whose telephone number is (571) 272-4445. The examiner can normally be reached on 8.30 a.m. to 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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PRIMARY EXAMINER